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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional): 30436.58USU1

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on July 26, 2007

Signature: Renato Marco Domingo

Typed or printed name: Renato Marco Domingo

Application Number	Filed
10/057,288	January 25, 2002

First Named Inventor: Christian P. Larsen

Art Unit	Examiner
1644	Phillip Gambel, Ph.D.

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

- ☐ applicant/inventor.
- ☐ assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)
- ☑ attorney or agent of record. Registration number 34,470
- ☐ attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34 _____

Sarah B. Adriano
Signature

Sarah B. Adriano
Typed or printed name

(626) 395-7801
Telephone number

July 26, 2007
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☑ *Total of 1 forms are submitted.

This collection of information is required by 35 U.S.C. 132. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11, 1.14 and 41.6. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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ATTACHMENT TO THE PRE-APPEAL BRIEF REQUEST FOR REVIEW

CLAIMS AND APPLICANTS' INVENTION

1. Independent claims 1, 9, 34, 55, 56, 62 and 63 as well as dependent claims 2, 5-6, 10, 12-13, 30, 33, 36-37, 44-52, 54, 57-60 and 64-74 are pending and rejected. These claims were previously presented in the Office Action response filed on December 13, 2006 at pages 3-13.

2. Applicants' invention, as shown in independent claims 1, 9, 34, 55 and 56 provides methods for inhibiting or reducing rejection of a solid organ or tissue/cellular transplant in a subject comprising the following sequence of steps: administering T cell depleted bone marrow cells to the subject before, during or after the solid organ or tissue/cellular transplant; administering an alkylating agent (e.g., busulfan) to the subject in an amount that facilitates mixed chimerism; administering a subsequent dose of T cell depleted bone marrow. Additionally, an immunosuppressive composition that blocks T cell costimulatory signals is administered in the subject before, during or after the transplant.

3. The present invention, as shown in independent claims 62 and 63, also provides methods for inhibiting or reducing rejection of solid organ or tissue/cellular transplant in a subject comprising administering: two doses of T cell depleted bone marrow, an immunosuppressive composition that blocks T cell costimulatory signals, and an alkylating agent at specific dosages.

PRIORITY

At pages 3-4 of the March 29, 2007 Office Action, the Office maintained the position that the filing date of the instant claims is deemed to be the filing date of priority application U.S. Serial No. 60/303,142, filed July 5, 2001, rather than priority application U.S. Serial No. 60/264,528, filed January 26, 2001.

Applicants' Argument

Applicants rebutted the Office's position in Office Action responses filed on (i) August 29, 2005 at pages 19-20, (ii) March 24, 2006 at pages 17-19 and (iii) December 13, 2006 at pages 16-18.

REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

At pages 4-7 of the March 29, 2007 Office Action, the Office maintained the rejection of claims 47-48 alleging that while the specification is enabling for the specific mutant CTLA4 molecules, such as the L104EA29YIg molecule disclosed in the specification as filed, it does not reasonably provide enablement for any "CTLA4 mutant molecule," to be employed as an immunosuppressive agent in the instant claimed methods.

Applicants' Argument

Applicants have previously rebutted the Office's position in Office Action responses filed on (i) August 29, 2005 at pages 21-22, (ii) March 24, 2006 at pages 21-22 and (iii) December 13, 2006 at pages 18-19. Applicants contend that the Office has rejected these claims in error because Applicants have met the legal standard for 35 U.S.C. §112, first paragraph, as described in the aforementioned Office Action responses.

There is no undue experimentation

1. Applicants provided methods for screening CTLA4 mutants for their binding capacity (Example 9, pages 71-83, of the originally filed application).
2. Applicants provided examples of about twenty-three mutant molecules (pages 35-36), over thirty mutation sites (Tables I and II at pages 82 and 83, respectively, and page 70, lines 21-25), including the entire nucleotide sequences of at least five of the mutants (SEQ ID NOs: 1, 3, 5, 7, 9), and described the required functions for other members of the class of proteins (page 75, line 28 through page 78, line 13; and page 79, line 20 through page 81).
3. Despite the fact that Applicants do not disclose every known CTLA4 mutant molecule, the identification of other species in the class would not entail undue experimentation, because Applicants' disclosure outlines a number of different assays for the identification of CTLA4 mutant molecule as claimed.

REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

At page 8 of the March 29, 2007 Office Action, the Office maintained the rejection of claims 67-70 under 35 U.S.C. §112, first paragraph, and is requiring Applicants to provide assurance that the ATCC deposits of the biological materials be made readily obtainable to the public. Additionally, the Office is requiring the Applicants to amend the specification to recite the date of deposit and the complete name and address of the depository.

Applicants' Argument

Applicants have complied with the Office. In the Office Action response filed on December 13, 2006 at pages 19-21, Applicants amended the specification to recite the name and complete address of the depository (page 2 of the December 13, 2006 Office Action response) and have provided a Statement of ATCC deposit, wherein Applicants state that "...all restrictions on the availability to the public of the materials deposited under ATCC Accession Nos. 68629 and CRL-10762 will be irrevocably removed upon the issuance of a patent from the present application"(page 21, second full paragraph of the Office Action response filed on December 13, 2006). If the Office requires any further affirmation, Applicants are amenable to comply with the Office's requirements.

REJECTION UNDER 35 U.S.C. §103(a)

(A) At pages 9-16 of the March 29, 2007 Office Action, the Office maintained the rejection of claims 1-6, 9-13, 17, 30, 33-37, 44-52, 54-63 and 64 as allegedly unpatentable over Sykes et al. (U.S. Patent No. 6,514,513), in view of:
(a) art known practice and modes of administration of alkylating agents such as busulfan/cyclophosphamide at various times to meet the needs of the patients, as acknowledged on pages 26-27 of the originally-filed specification *as evidenced by*:
(i) Andersson et al. (U.S Patent Nos. 5,430,057 and 5,559,148);
(ii) Hassan et al. (Blood, 1994, 84:2144-2150);
(iii) The Merck Manual of Diagnosis and Therapy, 17th Ed. (pages 1067-1074);
(iv) Shichi et al., (U.S. Patent No. 4,843,092);
(v) Strom et al. (Therapeutic Immunology, 1996, pages 451-456);
(vi) Sykes et al. (Nature Medicine, 1997, 3:783-787);
(vii) Wekerle et al. (J Exp Med, 1998, 187:2037-2044); and
(viii) Slattery et al (Therapeutic Drug Monitoring, 1998, 20:543-549).

(B) At pages 17-18 of the March 29, 2007 Office Action, the Office maintained the rejection of claims 1, 9 and 33 as allegedly unpatentable over Sykes et al. (U.S. Patent No. 6,514,513) in view of (a) and (i)-(viii) above and in view of Larsen et al. (U.S Patent No. 5,916,560).

(C) At pages 18-19 of the March 29, 2007 Office Action, the Office maintained the rejection of claims 1, 5, 6, 9-10, 12-23, 30, 34, 36-37, 44-52, 54-60, 62-63 and 64-74 as allegedly unpatentable over Sykes et al. (U.S. Patent No. 6,514,513) in view of (a) and (i)-(viii) above and in view of Peach et al. (US 2002/0182211)

Applicants' Argument

Applicants have previously rebutted the Office's position in Office Action responses filed on (i) August 29, 2005 at pages 27-32; (ii) March 24, 2006 at pages 23-35; and (iii) December 13, 2006 at pages 22-39. The teaching of Sykes et al. has been described in all three of the aforementioned Office Action responses. The teachings of the prior art references (i) – (viii) above have been described in the Office Action responses filed on March 24, 2006 and December 13, 2006.

Applicants contend that the Office has rejected these claims in error because the Office has not established a *prima facie* case for obviousness, as discussed in Office Action responses dated March 24, 2006 and December 13, 2006.

The references in combination do not teach or suggest the claimed steps

The Examiner asserts that the claimed method is an obvious modification of the Sykes reference. However, as discussed in Office Action responses dated March 24, 2006 and December 13, 2006, the prior art references alone or in combination, do not teach or suggest the claim

limitations, in the order claimed, namely, steps a-d of independent claims 1, 9, 34, 55, 56, 62 or 63 (see Office Action response dated December 13, 2006, pages 22-36).

There was no suggestion to modify the prior art in order to obtain the claimed invention.

To establish a *prima facie* case of obviousness, the Examiner must present evidence that one skilled in the art would have been led to arrive at the claimed invention. *Ex parte Levengood,* 28 U.S.P.Q.2d 1300 (BPAI 1993). Mere unsupported arguments cannot take the place of evidence. *In re Wiseman*, 596 F.2d 1019, 201 U.S.P.Q. 658, 661 (CCPA 1979).

In this regard, Sykes merely suggests that other methods of creating hematopoietic space, e.g., administering hematopoietic space creating antibodies or drugs, e.g., cyclophosphamide or busulfan, to the recipient, can be used (513 patent at column 5, lines 3-5). Without more, this statement cannot suggest the claimed invention. Merely desiring an end result does not constitute a specific modification of the prior art.

At page 11 of the March 29, 2007 Office Action, the Office asserts that Hassan et al. state that the therapeutic efficacy for busulfan/cyclophosphamide is considered to be equivalent, if not superior to cyclophosphamide and total body irradiation. Respectfully, the Office misses the point. It is the combination of busulfan and cyclophosphamide that are considered to be equivalent or superior to TBI. In fact, Hassan et al. *teach away* from the claimed methods because Hassan et al. teach that there is an increased transplant-related mortality associated with busulfan without cyclophosphamide.

Similarly, Slattery et al. teach that high levels of busulfan have been shown to increase the chance for severe hepatic veno-occlusive disease, for which there is no treatment and which can be fatal. Low levels of busulfan are associated with recurrence of chronic myeloid leukemia, whereas even lower levels of busulfan are associated with graft rejection. The therapeutic window for busulfan is narrow and disease and graft-source dependent. Similar to Hassan et al., Slattery et al. *teach away* from the claimed methods.

There is no evidence that any modification of the prior art would have led to a reasonable expectation of success in practicing the claimed invention.

Sykes provides only a cursory statement of replacing irradiation with busulfan as a preparative regimen for bone marrow transplants (BMT). This is very different from the claimed methods of inhibiting solid organ transplants. None of the cited references, alone, or in combination, provides guidance for modifying the methods to achieve therapeutically effective methods as claimed. In fact, Hassan et al. teach that total body irradiation is superior to busulfan in terms of patient survival. Moreover, there was no reason to believe that busulfan dosages of the art as a preparative regimen for BMT would be extrapolatable for busulfan dosages for facilitating mixed hematopoietic chimerism (MHC) in connection with solid organ transplants. Such cursory statements are not equivalent to a reasonable expectation of success because there was no direction or guidance on how to proceed to achieve the prophetic goal based on the references.

Additionally, Sykes does not teach any therapeutic administration sequence. The claimed method requires: administration of T cell depleted bone marrow to a subject; administration of an alkylating agent after the T cell depleted bone marrow to a subject; administration of additional T cell depleted bone marrow after the alkylating agent to a subject; administration of costimulatory blockade before, during and/or after the transplant.

Sykes fails to teach the use of busulfan together with other agents of the claimed methods for facilitating mixed hematopoietic chimerism, and the effective dosage of busulfan for such use. Additionally, Sykes fails to teach the therapeutic sequence of the claimed method.

The Examiner has not provided evidence that the prior art teaches or suggests as a whole the claimed methods. The claimed methods cannot be obvious over the cited references, because there was no suggestion regarding how to modify the prior art, in order to achieve the claimed methods. Moreover, even if it were obvious to try the combination of elements claimed, without a reasonable expectation of success, a *prima facie* case of obviousness cannot be made.

The claimed invention possesses unexpected advantages that the cited references do not teach

Applicants provided post filing confirmatory data showing that the methods of the invention possess superior properties (Office Action response dated December 13, 2006 at pages 35-36). Specifically, Applicants provided the following:

1. L. Kean et al.

   Here the authors show that nonmyeloablative preconditioning with busulfan (20mg/kg) coupled with costimulation blockade (CTLA4-Ig and anti-CD40L) can safely produce stable white blood cell (WBC) mixed chimerism and total replacement of the peripheral red cell compartment, resulting in a phenotypic cure of murine SCD.

2. Z. Guo et al.

   The results of these studies demonstrate that the infusion of donor bone marrow together with busulfan and costimulation blockade (anti-CD40L mAb and CTLA4-Ig) induces hematopoietic chimerism and promotes the long-term survival of intestinal allografts.

3. N. Shirasugi et al.

   A regimen consisting of CTLA4-Ig, anti-CD40L, donor BMCs, and a minimally myelosuppressive dose of busulfan produced stable donor-specific tolerance, and prevented both early and late cellular infiltration and chronic allograft vasculopathy, despite the rigorous rechallenge of a donor skin graft.